[redacted] 1647 16[redacted]

OIPE

SYSTEMS BRANCH

#14

CRF Problem Report

The Scientific and Technical Information Center (STIC) experienced a problem when processing the following computer readable form (CRF):

Application Serial Number: 09/454,223A
Filing Date: 12/9/1999
Date Processed by STIC: 2/10/2002

RECEIVED
MAR 04 2002
TECH CENTER 1600/2900

STIC Contact: **Mark Spencer, 703-308-4212**

Nature of Problem:

The CRF (was):

__✓__ (circle one) Damaged or Unreadable (for Unreadable, see attached)
____ Blank (no files on CRF) (see attached)
____ Empty file (filename present, but no bytes in file) (see attached)
____ Virus-infected. Virus name: _____ The STIC will not process the CRF.
____ Not saved in ASCII text
____ Sequence Listing was embedded in the file. According to Sequence Rules, submitted file should **only** be the Sequence Listing.
____ Did not contain a Sequence Listing. (see attached sample)
____ Other:

_____

PLEASE USE THE CHECKER VERSION 3.1 PROGRAM TO REDUCE ERRORS.
SEE BELOW FOR ADDRESS:
http:/www.uspto.gov/web/offices/pac/checker

Applicants submitting genetic sequence information electronically on diskette or CD-Rom should be aware that there is a possibility that the disk/CD-Rom may have been affected by treatment given to all incoming mail.
Please consider using alternate methods of submission for the disk/CD-Rom or replacement disk/CD-Rom.
Any reply including a sequence listing in electronic form should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office, and instead should be sent via the following to the indicated addresses:

1. EFS-Bio (<**http://www.uspto.gov/ebc/efs/downloads/documents.htm**> , **EFS Submission User Manual** - ePAVE)
2. **U.S. Postal Service**: U.S. Patent and Trademark Office, Box Sequence, P.O. Box 2327, Arlington, VA 22202
3. **Hand Carry directly to:**
   U.S. Patent and Trademark Office, Technology Center 1600, Reception Area, 7th Floor, Examiner Name, Sequence Information, Crystal Mall One, 1911 South Clark Street, Arlington, VA 22202
   Or
   U.S. Patent and Trademark Office, Box Sequence, Customer Window, Lobby, Room 1B03, Crystal Plaza Two, 2011 South Clark Place, Arlington, VA 22202
4. **Federal Express, United Parcel Service , or other delivery service to:** U.S. Patent and Trademark Office, Box Sequence, Room 1B03-Mailroom, Crystal Plaza Two, 2011 South Clark Place, Arlington, VA 22202

Revised 01/29/2002

=> s tumor necrosis factor super family? or TNFSF?
438571 TUMOR
199593 TUMORS
532938 TUMOR
(TUMOR OR TUMORS)
116367 NECROSIS
1 NECROSISES
116368 NECROSIS
(NECROSIS OR NECROSISES)
488334 FACTOR
1386205 FACTORS
1704284 FACTOR
(FACTOR OR FACTORS)
3941 SUPER
1 SUPERS
3942 SUPER
(SUPER OR SUPERS)
272263 FAMILY?
0 TUMOR NECROSIS FACTOR SUPER FAMILY?
(TUMOR(W)NECROSIS(W)FACTOR(W)SUPER(W)FAMILY?)
9 TNFSF?
L3 9 TUMOR NECROSIS FACTOR SUPER FAMILY? OR TNFSF?
=> s trimer or multimer
2051 TRIMER
1454 TRIMERS
3121 TRIMER
(TRIMER OR TRIMERS)
683 MULTIMER
1552 MULTIMERS
2024 MULTIMER
(MULTIMER OR MULTIMERS)
L4 5080 TRIMER OR MULTIMER

=> s l3 and l4
L5 0 L3 AND L4

=> d l3 1- ibib, abs
YOU HAVE REQUESTED DATA FROM 9 ANSWERS - CONTINUE? Y/(N):y

L3 ANSWER 1 OF 9 MEDLINE
ACCESSION NUMBER: 2001325905 MEDLINE
DOCUMENT NUMBER: 21214384 PubMed ID: 11313471
TITLE: DR3 regulates negative selection during thymocyte development.
AUTHOR: Wang E C; Thern A; Denzel A; Kitson J; Farrow S N; Owen M J
CORPORATE SOURCE: Imperial Cancer Research Fund, Lincoln's Inn Fields, London WC2A 3PX, United Kingdom.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2001 May) 21 (10) 3451-61. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607
AB DR3 (Ws1, Apo3, LARD, TRAMP, TNFSFR12) is a member of the death domain-containing tumor necrosis factor receptor (TNFR) superfamily, members of which mediate a variety of developmental events including the regulation of cell proliferation, differentiation, and apoptosis. We have investigated the in vivo role(s) of DR3 by generating mice congenitally deficient in the expression of the DR3 gene. We show that negative selection and anti-CD3-induced apoptosis are significantly impaired in DR3-null mice. In contrast, both superantigen-induced negative selection and positive selection are normal. The pre-T-cell receptor-mediated checkpoint, which is dependent on TNFR signaling, is also unaffected in DR3-deficient mice. These data reveal a nonredundant in vivo role for this TNF receptor family member in the removal of self-reactive T cells in the thymus.

L3 ANSWER 2 OF 9 MEDLINE
ACCESSION NUMBER: 2001192898 MEDLINE
DOCUMENT NUMBER: 21104552 PubMed ID: 11160623
TITLE: Pharmacokinetics and immunological effects of exogenously administered recombinant human B lymphocyte stimulator (BLyS) in mice.
AUTHOR: Parry T J; Riccobene T A; Strawn S J; Williams R; Daoud R; Carrell J; Sosnovtseva S; Miceli R C; Poortman C M; Sekut L; Li Y; Fikes J; Sung C
CORPORATE SOURCE: Human Genome Sciences, Rockville, Maryland 20850, USA.. tom_parry@hgsi.com
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2001 Feb) 296 (2) 396-404.
Journal code: JP3; 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405
AB B lymphocyte stimulator (BLyS; also known as TNFSF20, BAFF, TALL-1, zTNF4, and THANK), a tumor necrosis factor ligand family member, has recently been identified as a factor that promotes expansion and differentiation of the B cell population, leading to increases in serum immunoglobulin levels. Here, pharmacokinetic parameters for BLyS administered i.v. and s.c. to mice are described, and the effects of different dosing regimens on serum and salivary immunoglobulin levels as well as splenic cell populations are reported. The pharmacokinetics of BLyS following i.v. injection are monophasic with a half-life of 160 min, a clearance of 0.22 ml/min-kg, and a volume of distribution of 53 ml/kg. Systemic administration of BLyS to mice resulted in increased serum IgG, IgA, IgM, and IgE and salivary IgA as well as splenic B cell population expansion and differentiation. The i.v. and s.c. routes of administration were pharmacologically equivalent, even though s.c. bioavailability of BLyS is only 25%. BLyS (s.c.) dramatically elevated serum IgG and IgA levels, and the duration of the responses after cessation of treatment (t(1/2) = 4.4 and 1.3 days, respectively) are similar to the half-lives of endogenous IgG and IgA in mice. The IgM response is more modest than that of IgG and IgA but lasts longer (t(1/2) = 7.0 days) than the half-life of endogenous IgM. A linear pharmacodynamic response was identified between days of dosing x log(dose), and increases in serum IgG, IgA, and IgM indicating that the response is more sensitive to the duration of dosing than to the cumulative dose. The implications of these findings for therapeutic administration of BLyS are discussed.

L3 ANSWER 3 OF 9 MEDLINE
ACCESSION NUMBER: 2001033123 MEDLINE
DOCUMENT NUMBER: 20501097 PubMed ID: 11046022
TITLE: TGF-beta 1 and IFN-gamma direct macrophage activation by TNF-alpha to osteoclastic or cytocidal phenotype.
AUTHOR: Fox S W; Fuller K; Bayley K E; Lean J M; Chambers T J
CORPORATE SOURCE: Department of Experimental Pathology, St. George's Hospital Medical School, London, United Kingdom.
SOURCE: JOURNAL OF IMMUNOLOGY, (2000 Nov 1) 165 (9) 4957-63.
Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001130
AB TNF-related activation-induced cytokine (TRANCE; also called receptor activator of NF-kappaB ligand (RANKL), osteoclast differentiation factor (ODF), osteoprotegerin ligand (OPGL), and TNFSF11) induces the differentiation of progenitors of the mononuclear phagocyte lineage into

osteoclasts in the presence of M-CSF. Surprisingly, in view of its potent ability to induce inflammation and activate macrophage cytocidal function, TNF-alpha has also been found to induce osteoclast-like cells in vitro under similar conditions. This raises questions concerning both the nature of osteoclasts and the mechanism of lineage choice in mononuclear phagocytes. We found that, as with TRANCE, the macrophage deactivator TGF-beta(1) strongly promoted TNF-alpha-induced osteoclast-like cell formation from immature bone marrow macrophages. This was abolished by IFN-gamma. However, TRANCE did not share the ability of TNF-alpha to activate NO production or heighten respiratory burst potential by macrophages, or induce inflammation on s.c. injection into mice. This suggests that TGF-beta(1) promotes osteoclast formation not only by inhibiting cytocidal behavior, but also by actively directing TNF-alpha activation of precursors toward osteoclasts. The osteoclast appears to be an equivalent, alternative destiny for precursors to that of cytocidal macrophage, and may represent an activated variant of scavenger macrophage.

L3 ANSWER 4 OF 9 MEDLINE
ACCESSION NUMBER: 2001011234 MEDLINE
DOCUMENT NUMBER: 20409181 PubMed ID: 10951393
TITLE: Regulation of the differentiation and function of osteoclasts.
AUTHOR: Chambers T J
CORPORATE SOURCE: Department of Histopathology, St George's Hospital Medical School, London, UK.. t.chambers@sghms.ac.uk
SOURCE: JOURNAL OF PATHOLOGY, (2000 Sep) 192 (1) 4-13. Ref: 127
Journal code: JLB. ISSN: 0022-3417.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001024
AB The osteoclast is the cell that resorbs bone. It has been known for many years that its formation and function are regulated by cells of the osteoblastic lineage. Recently the molecular basis for this regulation was identified; osteoblastic cells induce osteoclastic differentiation and resorptive activity through expression of tumour necrosis factor (TNF) activation-induced cytokine (TRANCE) (also known as RANKL, ODF, OPGL, and TNFSF11), a novel membrane-inserted member of the TNF superfamily. Osteoclastic regulation is assisted through secretion of an inhibitor, osteoprotegerin (OPG) (OCIF, TNFRSF11B), a soluble (decoy) receptor for TRANCE. Osteoclast formation and survival also depend on and are substantially enhanced by transforming growth factor-beta (TGF-beta), which is abundant in bone matrix. Surprisingly, not only TRANCE but also TNF-alpha can induce osteoclast formation in vitro from bone marrow-derived mononuclear phagocytes, especially in the presence of TGF-beta. Whether or not TNF-alpha does the same in vivo, its ability to generate osteoclasts in vitro has significant implications regarding the nature of osteoclasts and their relationship to other mononuclear phagocytes, and a possible wider role for TRANCE in macrophage pathobiology. A hypothesis is presented in which the osteoclast is a mononuclear phagocyte directed towards a debriding function by TGF-beta, activated for this function by TRANCE, and induced to become specifically osteoclastic by the characteristics of the substrate or signals from bone cells that betoken such characteristics.

L3 ANSWER 5 OF 9 MEDLINE
ACCESSION NUMBER: 2000437941 MEDLINE
DOCUMENT NUMBER: 20439387 PubMed ID: 10985254
TITLE: The emerging role of CD40 ligand in HIV infection.
AUTHOR: Kornbluth R S
CORPORATE SOURCE: Department of Medicine, University of California San Diego and the VA San Diego Healthcare System, La Jolla 92093,

USA.
CONTRACT NUMBER: AI36214 (NIAID)
HL57911 (NHLBI)
SOURCE: JOURNAL OF LEUKOCYTE BIOLOGY, (2000 Sep) 68 (3) 373-82.
Ref: 118
Journal code: IWY; 8405628. ISSN: 0741-5400.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000915

AB CD40 ligand (also called CD40L, CD154, or TNFSF5) is a membrane protein expressed mainly by activated CD4+ T cells, which interacts with its receptor, CD40, on a variety of cells. The crucial importance of the CD40L-CD40 system for many immune responses has been extensively described. This review focuses on the multiple roles that this system may play in HIV infection. In early HIV infection, CD40L expression contributes to the immunological control of viral replication by inducing HIV-suppressive chemokines and supporting the production of anti-HIV antibodies and cytotoxic T cells. However, by activating antigen-presenting cells, such as dendritic cells and macrophages, CD40L can also lead to increased CD4+ T cell activation, which promotes the replication of HIV in these lymphocytes. Later, with the development of AIDS, CD40L-expressing CD4+ T cells become selectively depleted, perhaps as a result of a gp120-induced signal through CD4 that down-regulates CD40L expression. This acquired CD40L deficiency may explain the similarity between the types of opportunistic infections that occur in AIDS and in congenital CD40L deficiency. Vaccines or other strategies that promote the growth of CD4+ T cells capable of expressing CD40L may help to sustain host immunity against HIV and prevent AIDS-defining opportunistic infections.

L3 ANSWER 6 OF 9 MEDLINE
ACCESSION NUMBER: 2000386353 MEDLINE
DOCUMENT NUMBER: 20354998 PubMed ID: 10894944
TITLE: Molecular cloning and characterization of a mouse homolog of human TNFSF14, a member of the TNF superfamily.
AUTHOR: Misawa K; Nosaka T; Kojima T; Hirai M; Kitamura T
CORPORATE SOURCE: Department of Hematopoietic Factors, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan.
SOURCE: CYTOGENETICS AND CELL GENETICS, (2000) 89 (1-2) 89-91.
Journal code: DXK; 0367735. ISSN: 0301-0171.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB029155
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000809

AB A member of the tumor necrosis factor (TNF) superfamily, human TNFSF14 (hTNFSF14)/HVEM-L (herpes virus entry mediator ligand) was isolated as a cellular ligand for HVEM/TR2 and human lymphotoxin beta receptor (LTbetaR). TNFSF14 induces apoptosis and suppresses tumor formation. We have isolated a cDNA clone for a mouse homologue of hTNFSF14 by signal sequence trap (SST) screening which we recently developed. The deduced amino acid sequence of the mouse TNFSF14 (mTNFSF14) cDNA comprised 239 amino acid residues and was 77% identical to the hTNFSF14 protein. In Northern blot analysis, 2.1 kb and 4.2kb mTNFSF14 transcripts were detected in spleen and lung, and in heart, respectively. Fluorescence in situ hybridization analysis localized the mTNFSF14 gene Tnfsf14 to chromosome 17 which is tightly linked with Tnf, Lta, and Ltb.

L3 ANSWER 7 OF 9 MEDLINE
ACCESSION NUMBER: 2000125515 MEDLINE
DOCUMENT NUMBER: 20125515 PubMed ID: 10661873
TITLE: Characterization of a new member of the TNF family expressed on antigen presenting cells.
AUTHOR: Tribouley C; Wallroth M; Chan V; Paliard X; Fang E; Lamson G; Pot D; Escobedo J; Williams L T
CORPORATE SOURCE: Chiron Corporation, Emeryville, CA 94608-2916, USA.
SOURCE: BIOLOGICAL CHEMISTRY, (1999 Dec) 380 (12) 1443-7. Journal code: CK4; 9700112. ISSN: 1431-6730.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF166695
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000307
AB The TNF family is involved in the regulation of the immune system, and its members have been implicated in a variety of biological events such as apoptosis, cell proliferation, differentiation and survival. Here we present a new member of the TNF family, tumor necrosis factor superfamily member 20 (TNFSF20) that we have identified from the expressed sequence tag (EST) database and characterized. The human protein is a 285 amino acid long type II transmembrane protein and is 19% homologous to TNF in its extra-cellular domain. TNFSF20 is expressed at the surface of antigen presenting cells such as cells of the macrophagemonocyte lineage and dendritic cells. After treatment with bacterial lipopolysaccharide (LPS), TNFSF20 expression is downregulated at the surface of the expresssing cells, suggesting that the membrane-bound protein gets cleaved, and that a soluble factor is released in the extra-cellular compartment. The soluble form of the recombinant TNFSF20 induces proliferation of resting peripheral blood monocytes (PBMC) and cell death of activated lymphocytes. TNFSF20 might therefore play a critical role in the regulation of cell-mediated immune responses.

L3 ANSWER 8 OF 9 MEDLINE
ACCESSION NUMBER: 2000099006 MEDLINE
DOCUMENT NUMBER: 20099006 PubMed ID: 10630977
TITLE: Ionizing radiation alters Fas antigen ligand at the cell surface and on exfoliated plasma membrane-derived vesicles: implications for apoptosis and intercellular signaling.
AUTHOR: Albanese J; Dainiak N
CORPORATE SOURCE: Department of Medicine, Bridgeport Hospital, Yale University School of Medicine, Bridgeport, Connecticut 06610, USA.
SOURCE: RADIATION RESEARCH, (2000 Jan) 153 (1) 49-61. Journal code: QMP; 0401245. ISSN: 0033-7587.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127
AB Resident proteins that reside on the plasma membrane are continually exfoliated from the cell surface. Exfoliation is a selective, energy-dependent process that mediates intercellular communication. Ionizing radiation modulates the expression of many plasma membrane-bound growth regulators, including the "death" ligand, TNFSF6 (formerly known as FasL, CD95L). Here we report that ionizing radiation induces dose-dependent up-regulation of TNFSF6 on plasma membranes purified from SW620 cells, a TNFSF6-expressing colon cancer cell line. Serum-free medium conditioned by exposed and control cells was collected and exfoliated vesicles were obtained by

ultracentrifugation. Western blot analysis of vesicles from unexposed cells and from cells treated with 10 Gy showed increased amounts of TNFSF6 compared to that on vesicles from unexposed cells. Cells treated with 4 Gy released vesicles having a low level of TNFSF6 on their surface relative to that on vesicles exfoliated from unexposed cells. When assayed for bioactivity, vesicles from unexposed cells induced the greatest level of apoptosis in TNFRSF6 (formerly known as FAS) receptor-bearing Jurkat cells (cell surviving fraction of 43.7 +/- 6.1; P < 0.05), followed by vesicles collected from cells treated with 4 Gy (79.6 +/- 2.6%; P < 0.05). Despite having a high level of TNFSF6 by Western analysis, vesicles collected from cells exposed to 10 Gy display minimal biological activity (77.9 +/- 3.2%; P < 0.05), suggesting that modification of the vesicle-associated ligand has occurred. Our results indicate that ionizing radiation increases the level of TNFSF6 exfoliated on extracellular vesicles. The data may provide a mechanism for abscopal and bystander effects after irradiation.

L3 ANSWER 9 OF 9 MEDLINE
ACCESSION NUMBER: 2000054362 MEDLINE
DOCUMENT NUMBER: 20054362 PubMed ID: 10585776
TITLE: Characterization of TNFRSF19, a novel member of the tumor necrosis factor receptor superfamily.
AUTHOR: Hu S; Tamada K; Ni J; Vincenz C; Chen L
CORPORATE SOURCE: Mayo Graduate and Medical Schools, Mayo Clinic, Rochester, Minnesota 55905, USA.
SOURCE: GENOMICS, (1999 Nov 15) 62 (1) 103-7.
Journal code: GEN; 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF173166
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000204
AB By searching the expressed sequence tag database, a novel murine tumor necrosis factor receptor designated TNFRSF19 was identified. TNFRSF19 cDNA encodes a putative membrane protein of 348 amino acids with one incomplete and two complete cysteine-rich motifs within its extracellular region and a large cytoplasmic domain. TNFRSF19 mRNA can be detected in most murine tissues examined, particularly in brain, reproductive organs, and late developmental stages of murine embryo, but not in tissues of the immune system. The cell surface expression of the ligand of TNFRSF19 is highly restricted. Of 22 human and murine cell lines examined by FACS analysis, only Raji (B cell lymphoma cell line), GM847 (fibroblast cell line), 293 (embryonic kidney cell line), and K562 (chronic myeloid leukemia) were positive. TNFRSF19 did not bind newly cloned TNF ligands, including TWEAK (HGMW-approved symbol TNFSF12), VEGI/TL1 (HGMW-approved symbol TNFSF15), TL6/endokine (HGMW-approved symbol TNFSF18), APRIL (HGMW-approved symbol TNFSF13), OPGL (HGMW-approved symbol TNFSF11), LIGHT (HGMW-approved symbol TNFSF14), or BAFF/THANK (HGMW-approved symbol TNFSF13B) by enzyme-linked immunosorbent assay and FACS analyses. Overexpression of TNFRSF19 transduced neither apoptotic signaling nor signals leading to NF-kappaB induction. Taken together with the data that the TNFRSF19 extracellular domain-immunoglobulin fusion protein did not affect the allogeneic mixed lymphocyte reaction, our data indicate that TNFRSF19 is not involved in the modulation of immune responses.

=> s cd40l or cd154 or gp39 or t-bam or rankl or trance or opgl or odf or cd27l or cd70
913 CD40L
280 CD154
123 GP39
3010378 T
1002 BAM
17 BAMS
1009 BAM
(BAM OR BAMS)
9 T-BAM

(T(W)BAM)
115 RANKL
424 TRANCE
12 TRANCES
429 TRANCE
(TRANCE OR TRANCES)
51 OPGL
134 ODF
12 ODFS
142 ODF
(ODF OR ODFS)
69 CD27L
78 CD70
L6 1798 CD40L OR CD154 OR GP39 OR T-BAM OR RANKL OR TRANCE OR OPGL OR ODF OR CD27L OR CD70

=> s l6 and l4
L7 20 L6 AND L4

=> d l7 1- ibib,abs
L7 ANSWER 1 OF 20 MEDLINE
ACCESSION NUMBER: 2001361391 MEDLINE
DOCUMENT NUMBER: 21317403 PubMed ID: 11422906
TITLE: Maturation of dendritic cells by recombinant human CD40L-trimer leads to a homogeneous cell population with enhanced surface marker expression and increased cytokine production.
AUTHOR: Wurtzen P A; Nissen M H; Claesson M H
CORPORATE SOURCE: Department of Medical Anatomy, The Panum Institute, University of Copenhagen, Denmark.. P.Wurtzen@server.mai.ku.dk
SOURCE: SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (2001 Jun) 53 (6) 579-87.
Journal code: UCW; 0323767. ISSN: 0300-9475.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719
AB Dendritic cells (DC) have been shown to be potent inducers of specific cytotoxic T-cell responses both in vivo and in vitro. Furthermore, exposure to cytokines such as tumour necrosis factor (TNF)-alpha or CD40 triggering changes DC phenotype and cytokine production and may enhance the T-cell activating capacity of the DC. We studied DC phenotype and cytokine production as well as the T-cell proliferation and cytotoxic T lympocyte (CTL) activation induced by DC generated in vitro. In addition, the effect of exposure to recombinant human CD40L-trimer (huCD40LT) on these parameters was investigated. Effective differentiation of monocytes derived from freshly isolated peripheral blood mononuclear cells (PBMC) was obtained with granulocyte macrophage-colony stimulating factor (GM-CSF) and interleukin (IL)-4. The DC expression of human leucocyte antigen (HLA) molecules, CD80, CD83, and CD86 was markedly enhanced by exposure to huCD40LT even compared to TNF-alpha exposure. Only a moderate cytokine production was observed initially, while TNF-alpha addition or CD40 triggering, especially, induced enhanced production of IL-6 and IL-12 p40. Surprisingly, comparable induction of T-cell proliferation by a DC allostimulus or through the presentation of PPD, and influenza M1-peptide specific CTL activity was obtained with nonmaturated (CD83-) and maturated (CD83+) DC. In conclusion, a final maturation of monocyte-derived DC through huCD40LT resulted in a highly homogeneous cell population with enhanced surface marker expression and high production of pro-inflammatory cytokines. In addition, the induction of responses to allo or recall antigens presented by huCD40LT maturated DC was comparable to the responses obtained with the DC maturated through TNF-alpha exposure.

L7 ANSWER 2 OF 20 MEDLINE

ACCESSION NUMBER: 2001277851 MEDLINE
DOCUMENT NUMBER: 21265113 PubMed ID: 11372024
TITLE: Role of CD40 ligand signaling in defective type 1 cytokine response in human immunodeficiency virus infection.
AUTHOR: Subauste C S; Wessendarp M; Smulian A G; Frame P T
CORPORATE SOURCE: Division of Infectious Diseases, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio 45267-0560, USA.. carlos.subauste@uc.edu
CONTRACT NUMBER: AI-25897 (NIAID)
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (2001 Jun 15) 183 (12) 1722-31.
Journal code: IH3; 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010716
Last Updated on STN: 20010716
Entered Medline: 20010712
AB The pathogenesis of defective interleukin (IL)-12 and interferon (IFN)-gamma production in human immunodeficiency virus (HIV)-infected patients remains to be elucidated. This study investigated the possibility that perturbations in CD40 ligand signaling are involved in this defect. CD40 ligand trimer (CD40LT) stimulated peripheral blood mononuclear cell (PBMC) production of IL-12 in response to Toxoplasma gondii and cytomegalovirus (CMV). Regardless of the CD4 cell count, CD40LT restored IL-12 secretion in response to T. gondii in HIV-infected patients. In the presence of CD40LT, PBMC from both HIV-infected patients and control subjects produced high levels of IL-12 in response to CMV. CD40LT restored T. gondii- and CMV-triggered IFN-gamma secretion by T cells and PBMC from HIV-infected patients with a CD4 cell count >200 cells/microL. CD4 cells from HIV-infected patients, even those with a CD4 cell count >500 cells/microL, had defective CD40L induction after T cell stimulation mediated by antigen-presenting cells. Together, impaired CD40L induction is likely to contribute to defective IL-12 and IFN-gamma production in HIV infection.

L7 ANSWER 3 OF 20 MEDLINE
ACCESSION NUMBER: 2001267781 MEDLINE
DOCUMENT NUMBER: 21257784 PubMed ID: 11358428
TITLE: Coexpression of normal and mutated CD40 ligand with deletion of a putative RNA lariat branchpoint sequence in X-linked hyper-IgM syndrome.
AUTHOR: Zhu X; Chung I; O'Gorman M R; Scholl P R
CORPORATE SOURCE: Disease Pathogenesis Program, Children's Memorial Institute for Education and Research, Chicago, Illinois 60614, USA.
SOURCE: CLINICAL IMMUNOLOGY, (2001 Jun) 99 (3) 334-9.
Journal code: C90; 100883537. ISSN: 1521-6616.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20010625
Entered Medline: 20010621
AB We describe a novel CD40 ligand (CD40L) splicing mutation in a patient with X-linked hyper-IgM syndrome (X-HIM) associated with alternate splicing of exon 3, resulting in the expression of both full-length and exon-3-skipped CD40L mRNA. The mutation is an 8-bp deletion 25 bp upstream of the intron 2/exon 3 junction which overlaps a putative RNA branchpoint, suggesting that it may impair RNA lariat formation. The exon-3-skipped CD40L transcript encodes a truncated protein (CD40LDeltaE3) encompassing the cytoplasmic, transmembrane, and extracellular stalk domains, but lacking the CD40L receptor binding domain. CD40LDeltaE3 protein expression was readily detectable in transfected Cos cells by immunofluorescence. In cells cotransfected with CD40LDeltaE3 and wild-type CD40L, expression of CD40LDeltaE3 did not inhibit the expression of wild-type CD40L monomers, but

strongly inhibited staining by the conformationally sensitive anti-CD40L mAb 5c8, suggesting that CD40LDeltaE3 acts in a dominant negative manner to inhibit the assembly of functional CD40L trimers. This mechanism may contribute to the pathophysiology of CD40L deficiency in X-HIM patients with leaky splice site mutations. Copyright 2001 Academic Press.

L7 ANSWER 4 OF 20 MEDLINE
ACCESSION NUMBER: 2001202802 MEDLINE
DOCUMENT NUMBER: 21125714 PubMed ID: 11073939
TITLE: CD154 variant lacking tumor necrosis factor homologous domain inhibits cell surface expression of wild-type protein.
AUTHOR: Su L; Garber E A; Hsu Y M
CORPORATE SOURCE: Department of Protein Engineering, Biogen, Inc., Cambridge, Massachusetts 02142, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jan 19) 276 (3) 1673-6.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412
AB X-linked hyper-IgM (XHIM) syndrome is an immunological disorder resulting from mutations in the CD154 gene. Some mutations occur in splicing sites and result in transcripts encoding wild-type and mutant proteins. These mutants lack the tumor necrosis factor homologous (TNFH) domain and consequently fail to trimerize. Given that the TNFH domain is responsible for trimerization, one may predict that the TNFH mutant can not participate in the assembly of wild-type CD154. Thus, it was puzzling why these patients exhibit XHIM phenotype, presumably resulting from a lack of functional CD154. One possibility is that the TNFH mutant exhibits a dominant negative effect over the wild-type protein. To investigate this, we coexpressed the wild-type protein and a TNFH mutant and examined the biochemical and functional properties of the resulting CD154 products. We demonstrate that despite the lack of the TNFH domain, the TNFH mutant can associate with the wild-type protein. Furthermore, such an association compromises the ability of the wild-type protein to mature onto the cell surface. These results provide a mechanism for the defect of CD154 in XHIM patients producing both wild-type and TNFH variants and suggest that besides the TNFH domain, the stalk region participates in the assembly of CD154 trimers.

L7 ANSWER 5 OF 20 MEDLINE
ACCESSION NUMBER: 2001076370 MEDLINE
DOCUMENT NUMBER: 20523561 PubMed ID: 11071647
TITLE: A subset of human monocyte-derived dendritic cells expresses high levels of interleukin-12 in response to combined CD40 ligand and interferon-gamma treatment.
AUTHOR: Mosca P J; Hobeika A C; Clay T M; Nair S K; Thomas E K; Morse M A; Lyerly H K
CORPORATE SOURCE: Departments of General and Thoracic Surgery, Pathology, Immunology, and Internal Medicine, Center for Genetic and Cellular Therapies, Duke University Medical Center, Durham, NC, USA.
CONTRACT NUMBER: CA77894-02 (NCI)
MO1RR00030 (NCRR)
PO1 CA 78673 01A1 (NCI)
SOURCE: BLOOD, (2000 Nov 15) 96 (10) 3499-504.
Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200101

ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111

AB Dendritic cells (DCs) may arise from multiple lineages and progress through a series of intermediate stages until fully mature, at which time they are capable of optimal antigen presentation and T-cell activation. High cell surface expression of CD83 is presumed to correlate with full maturation of DCs, and a number of agents have been shown to increase CD83 expression on DCs. We hypothesized that interleukin 12 (IL-12) expression would be a more accurate marker of functionally mature DCs capable of activating antigen-specific T cells. We used combinations of signaling through CD40, using CD40 ligand trimer (CD40L), and interferon gamma to demonstrate that CD83 expression is necessary but not sufficient for optimal production of IL-12 by DCs. Phenotypically mature DCs could be induced to produce high levels of IL-12 p70 only when provided 2 simultaneous stimulatory signals. By intracellular cytokine detection, we determined that only a subset of cells that express high levels of CD80 and CD83 generate large amounts of IL-12. DCs matured with both signals are superior to DCs stimulated with the individual agents in activating antigen-specific T cell in vitro. These findings have important implications regarding the identification, characterization, and clinical application of functionally mature DCs.

L7 ANSWER 6 OF 20 MEDLINE
ACCESSION NUMBER: 2000488979 MEDLINE
DOCUMENT NUMBER: 20493508 PubMed ID: 11035950
TITLE: Expression, purification, and characterization of the human receptor activator of NF-kappaB ligand (RANKL) extracellular domain.
AUTHOR: Willard D; Chen W J; Barrett G; Blackburn K; Bynum J; Consler T; Hoffman C; Horne E; Iannone M A; Kadwell S; Parham J; Ellis B
CORPORATE SOURCE: Molecular Sciences Department, Structural Chemistry Department, Glaxo Wellcome, Inc., Five Moore Drive, Research Triangle Park, North Carolina 27709, USA.. dhw29438@glaxowellcome.com
SOURCE: PROTEIN EXPRESSION AND PURIFICATION, (2000 Oct) 20 (1) 48-57.
Journal code: BJV. ISSN: 1046-5928.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001129

AB Receptor activator of NF-kappaB ligand (RANKL) is a type II transmembrane protein found on osteoblasts which functions as a major determinant of osteoclast differentiation and activation. RANKL mediates bone homeostasis through binding to the cognate ligand on osteoclasts, RANK, and a soluble decoy receptor, osteoprotegerin (OPG). We designed a construct encoding the extracellular domain of human RANKL that conformed to reports of native processing. To encourage folding and posttranslational modification of a normally membrane-inserted moiety, we expressed the RANKL truncate as a secreted protein using the signal sequence from OPG in a Trichoplusia ni cell line using a baculovirus expression vector. RANKL was purified by a three-step process including an OPG-Fc affinity column. SDS-PAGE and mass spectral analysis indicated that the protein was >99% pure and glycosylated. Circular dichroism spectra revealed that the protein exhibited structural elements similar to tumor necrosis factor-alpha. By BIAcore analysis, RANKL bound to OPG with an affinity of 6.7 nM. Sedimentation equilibrium analytical ultracentrifugation analyses established that our protein existed as a trimer. We conclude that our expressed human RANKL truncate is folded, is functional, and exhibits self-association consistent with other family members.

L7 ANSWER 7 OF 20 MEDLINE
ACCESSION NUMBER: 2000469690 MEDLINE
DOCUMENT NUMBER: 20435353 PubMed ID: 10979969
TITLE: Soluble CD40 ligand induces selective proliferation of lymphoma cells in primary mantle cell lymphoma cell cultures.
AUTHOR: Andersen N S; Larsen J K; Christiansen J; Pedersen L B; Christophersen N S; Geisler C H; Jurlander J
CORPORATE SOURCE: Leukemia and Lymphoma Marker Laboratory, Department of Hematology, and the Finsen Laboratory, Rigshospitalet, Copenhagen, Denmark.. nanders@rh.dk
SOURCE: BLOOD, (2000 Sep 15) 96 (6) 2219-25.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001004
AB Interaction between CD40 and the CD40 ligand (CD40L) is critical for the survival and proliferation of B cells during immunopoiesis. However, the role of CD40L in the pathogenesis of malignant lymphomas is ambiguous. Primary mantle cell lymphoma (MCL) cells were cultured in the presence of recombinant human CD40L trimer (huCD40LT), and a significant time- and dose-dependent induction of DNA synthesis was observed in thymidine incorporation assays (n = 7, P <.04). The maximal rate of DNA synthesis was reached at huCD40LT doses of 100 ng/mL and above after 4 days of culture, but a significant increase of DNA synthesis was detected already at doses of 1 ng/mL (P =.03). HuCD40LT never inhibited the basal level of DNA synthesis. These findings established 400 ng/mL of huCD40LT for 4 days as standard conditions in the system. Under these conditions, huCD40LT significantly increased the proportion of cells in the S/G(2)/M phases of the cell cycle in 4 of 7 studied cases, while the fraction of apoptotic cells remained unchanged (n = 7). HuCD40LT also induced expression of CD80/B7-1, CD86/B7-2, and CD95/Fas and up-regulated the expression of HLA-DR (n = 6). With the use of bromodeoxyuridine incorporation in triple-color flow cytometric analysis, it was found that huCD40LT induced cell-cycle progression in light chain-restricted cells only, of which a median of 14% (range, 0.5% to 29%; n = 4) returned to G(0/1) phase DNA content after bromodeoxyuridine incorporation, demonstrating completion of at least one cell cycle in the presence of huCD40LT. Thus, primary clonal MCL cells are activated and can proliferate in the presence of huCD40LT as a single agent.

L7 ANSWER 8 OF 20 MEDLINE
ACCESSION NUMBER: 1999361824 MEDLINE
DOCUMENT NUMBER: 99361824 PubMed ID: 10435471
TITLE: Epitope-dependent synergism and antagonism between CD40 antibodies and soluble CD40 ligand for the regulation of CD23 expression and IgE synthesis in human B cells.
AUTHOR: Challa A; Pound J D; Armitage R J; Gordon J
CORPORATE SOURCE: MRC Centre for Immune Regulation, University of Birmingham, Edgbaston, UK.
SOURCE: ALLERGY, (1999 Jun) 54 (6) 576-83.
Journal code: 39C; 7804028. ISSN: 0105-4538.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990917
AB BACKGROUND: The induction of IgE synthesis in naive B cells requires two T-cell-derived signals: one delivered through CD40 and the other via interleukin-4 (IL-4). The natural counterstructure to CD40 is the CD40 ligand (CD40L). We have asked about the interplay between

CD40L and CD40 mAb that recognize distinct epitopes in delivering signals for regulating IL-4-dependent IgE synthesis and the expression of CD23, the low-affinity IgE receptor, in resting B cells. METHODS: After culture of purified human tonsillar B cells with CD40 agonists and IL-4, surface CD23 was determined by flow cytometric analysis. CD23 levels in cell lysates and supernatants were quantified by ELISA, as were those of secreted IgE. RESULTS: With regard to both induction of CD23 and IgE production, soluble CD40L trimer (sCD40LT) showed synergistic interaction with two mAb to CD40 which bind to epitopes located outside the ligand binding site (EA5 and 5C3), but not with a mAb (G28-5) which effectively competes for CD40L binding to CD40. Each of the two noncompeting mAb to CD40 was able to cooperate strongly with sCD40LT in promoting high-level induction of CD23 even in the absence of IL-4, an effect mirrored in the promotion of strong homotypic clustering and high-rate DNA synthesis. G28-5, uniquely, induced a down-regulation in IL-4-induced CD23 expression with time, a change that was accompanied by an increase in the amount of soluble CD23 detected. While the two noncompeting mAb consistently synergized with sCD40LT for the promotion of IL-4-dependent IgE synthesis, sCD40LT and G28-5 (which, by itself, was the most potent of the CD40 mAb at inducing IL-4-dependent IgE production) exhibited mutual antagonism in this regard, the level of which could be quite profound. CONCLUSIONS: This study demonstrates that appropriate targeting of CD40 can modulate IgE synthesis either positively or negatively.

L7 ANSWER 9 OF 20 MEDLINE
ACCESSION NUMBER: 1999282955 MEDLINE
DOCUMENT NUMBER: 99282955 PubMed ID: 10352287
TITLE: CD40-CD40 ligand interaction is central to cell-mediated immunity against Toxoplasma gondii: patients with hyper IgM syndrome have a defective type 1 immune response that can be restored by soluble CD40 ligand trimer.
AUTHOR: Subauste C S; Wessendarp M; Sorensen R U; Leiva L E
CORPORATE SOURCE: Division of Infectious Diseases, University of Cincinnati College of Medicine, OH 46267, USA.. carlos.subauste@uc.edu
CONTRACT NUMBER: AI37936 (NIAID)
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Jun 1) 162 (11) 6690-700. Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990616
AB Cell-mediated immunity that results in IL-12/IFN-gamma production is essential to control infections by intracellular organisms. Studies in animal models revealed contrasting results in regard to the importance of CD40-CD40 ligand (CD40L) signaling for induction of a type 1 cytokine response against these pathogens. We demonstrate that CD40-CD40L interaction in humans is critical for generation of the IL-12/IFN-gamma immune response against Toxoplasma gondii. Infection of monocytes with T. gondii resulted in up-regulation of CD40. CD40-CD40L signaling was required for optimal T cell production of IFN-gamma in response to T. gondii. Moreover, patients with hyper IgM (HIGM) syndrome exhibited a defect in IFN-gamma secretion in response to the parasite and evidence compatible with impaired in vivo T cell priming after T. gondii infection. Not only was IL-12 production in response to T. gondii dependent on CD40-CD40L signaling, but also, patients with HIGM syndrome exhibited deficient in vitro secretion of this cytokine in response to the parasite. Finally, in vitro incubation with agonistic soluble CD40L trimer enhanced T. gondii-triggered production of IFN-gamma and, through induction of IL-12 secretion, corrected the defect in IFN-gamma production observed in HIGM patients. Our results are likely to explain the susceptibility of patients with HIGM syndrome to infections by opportunistic pathogens.

L7 ANSWER 10 OF 20 MEDLINE
ACCESSION NUMBER: 1999255021 MEDLINE

DOCUMENT NUMBER: 99255021 PubMed ID: 10323442
TITLE: Elevated levels and functional capacity of soluble CD40 ligand in systemic lupus erythematosus sera.
AUTHOR: Vakkalanka R K; Woo C; Kirou K A; Koshy M; Berger D; Crow M K
CORPORATE SOURCE: Hospital for Special Surgery and Weill Medical College of Cornell University, New York, New York 10021, USA.
CONTRACT NUMBER: P50-AR-42588 (NIAMS)
R21-AI-28367 (NIAID)
RO1-AI-42185 (NIAID)
SOURCE: ARTHRITIS AND RHEUMATISM, (1999 May) 42 (5) 871-81.
Journal code: 90M; 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990521
AB OBJECTIVE: To measure soluble CD40 ligand (sCD40L) in sera from patients with systemic lupus erythematosus (SLE) and to study the functional capacity of sCD40L in mediating B cell activation. METHODS: A 2-site enzyme-linked immunosorbent assay (ELISA) was used to measure sCD40L in the sera of 66 SLE patients, 30 disease control patients, and 23 healthy subjects. Induction of B cell activation antigen expression was used to assess the functional capacity of sCD40L in SLE sera. RESULTS: The mean concentration of sCD40L was statistically significantly higher ($P < 0.0001$) in SLE patients than in disease controls or healthy subjects, and segregation of SLE patients by severe, moderate, or mild extent of disease showed a relationship between disease severity and sCD40L concentration. Western blot analysis demonstrated the presence of the 18-kd band of sCD40L in SLE sera, and the results of a 1-site ELISA protocol suggested that some of the product in SLE sera was present in dimer or trimer form. Functional studies showed that 10 ng/ml of recombinant CD40L, a level present in some SLE sera, induced increased expression of CD95 on B cells. Several SLE sera also induced CD95 or CD86 on Ramos B cells, a result that was inhibited by anti-CD40L monoclonal antibodies. CONCLUSION: The soluble form of CD40L is present in the sera of most patients with SLE and may have the capacity to mediate B cell activation. Aberrant expression of CD40L might be predicted to result in activation of bystander B cells, including those that have encountered self antigens, and to contribute to autoantibody secretion.

L7 ANSWER 11 OF 20 MEDLINE
ACCESSION NUMBER: 1999192794 MEDLINE
DOCUMENT NUMBER: 99192794 PubMed ID: 10092834
TITLE: Differential effects of CD40 ligand/trimer stimulation on the ability of dendritic cells to replicate and transmit HIV infection: evidence for CC-chemokine-dependent and -independent mechanisms.
AUTHOR: McDyer J F; Dybul M; Goletz T J; Kinter A L; Thomas E K; Berzofsky J A; Fauci A S; Seder R A
CORPORATE SOURCE: Clinical Immunology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Mar 15) 162 (6) 3711-7.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990413
AB The role of exogenous stimulation of CD40 by CD40 ligand (CD40L) in dendritic cell (DC) maturation, CC-chemokine production, and CCR5 receptor expression was examined using a soluble trimeric CD40L

agonist protein (CD40LT). Stimulation of monocyte-derived DCs with CD40LT enhanced the production of the CC-chemokines macrophage inflammatory protein (MIP)-1 alpha, MIP-1 beta, and RANTES and diminished surface expression of CCR5. Based on these findings, the functional role of CD40LT stimulation on the ability of DCs to replicate and transmit HIV viral infection was studied. The addition of CD40LT to cocultures of naive CD4+ T cells and autologous DCs (T/DC) infected with the macrophage-tropic isolate, HIVBaL, caused a striking reduction in reverse transcriptase (RT) activity after 10 and 14 days of culture. The addition of a mixture of Abs against CC-chemokines abrogated the decrease in RT activity, demonstrating that the inhibitory effect mediated by CD40LT was CC-chemokine-dependent. In contrast, the presence of CD40LT in T/DC cocultures infected with the T cell-tropic isolate, HIV IIIB, caused an increase in RT activity that was CC-chemokine-independent. Of note, CD40LT stimulation also inhibited RT activity in cultures containing macrophage-tropic virus (HIVBaL)-infected DC only. However, in contrast to the results seen in the T/DC cocultures, CD40LT stimulation inhibited RT activity in cultures of DCs alone in a CC-chemokine-independent manner. Together, these results show that CD40LT stimulation of DCs suppresses HIV replication and transmission to CD4+ T cells by two potentially different mechanisms.

L7 ANSWER 12 OF 20 MEDLINE
ACCESSION NUMBER: 1999074605 MEDLINE
DOCUMENT NUMBER: 99074605 PubMed ID: 9857288
TITLE: Leukocyte transfusion-associated granulocyte responses in a patient with X-linked hyper-IgM syndrome.
AUTHOR: Atkinson T P; Smith C A; Hsu Y M; Garber E; Su L; Howard T H; Prchal J T; Everson M P; Cooper M D
CORPORATE SOURCE: Department of Pediatrics, University of Alabama at Birmingham 35294, USA.
SOURCE: JOURNAL OF CLINICAL IMMUNOLOGY, (1998 Nov) 18 (6) 430-9. Journal code: HRC; 8102137. ISSN: 0271-9142.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990324
Last Updated on STN: 19990324
Entered Medline: 19990310
AB X-linked hyper-IgM syndrome (XHIM) is a severe congenital immunodeficiency caused by mutations in CD154 (CD40 ligand, gp39), the T cell ligand for CD40 on B cells. Chronic or cyclic neutropenia is a frequent complicating feature that heightens susceptibility to severe infections. We describe a patient with a variant of XHIM who produced elevated levels of serum IgA as well as IgM and suffered from chronic severe neutropenia. Eight of ten leukocyte transfusions with cells from a maternal aunt, performed because of mucosal infections, resulted in similar episodes of endogenous granulocyte production. Transfection studies with the mutant CD154 protein indicate that the protein is expressed at the cell surface and forms an aberrant trimer that does not interact with CD40. The data suggest that allogeneic cells from the patient's aunt, probably activated T cells bearing functional CD154, may interact with CD40+ recipient cells to produce maturation of myeloid precursors in the bone marrow.

L7 ANSWER 13 OF 20 MEDLINE
ACCESSION NUMBER: 1998438339 MEDLINE
DOCUMENT NUMBER: 98438339 PubMed ID: 9763568
TITLE: Prolonged phenotypic, functional, and molecular change in group I Burkitt lymphoma cells on short-term exposure to CD40 ligand.
AUTHOR: Baker M P; Eliopoulos A G; Young L S; Armitage R J; Gregory C D; Gordon J
CORPORATE SOURCE: Departments of Immunology and the Institute of Cancer Studies, University of Birmingham, Birmingham, UK.
SOURCE: BLOOD, (1998 Oct 15) 92 (8) 2830-43. Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981109

AB Group I Burkitt lymphoma (BL) cell lines (L3055, Elijah, Louckes, BL2, and BL29) retaining the original biopsy phenotype were found to undergo prolonged phenotypic, functional, and molecular change on short-term exposure to soluble recombinant CD40L trimer. Sensitivity to, extent of, and duration of change appeared to reflect passage number in that the earliest passaged lines, L3055 and BL29, were generally the most susceptible. Culture of group I BL lines with CD40L resulted in significant growth arrest (without apoptosis) that, for L3055 cells, was sustained for 7 to 9 days after 72 hours of exposure. This was accompanied by the formation of large homotypic aggregates together with gross changes in individual cell morphology and a concomitant upregulation of CD54 (ICAM-1). Three of the five group I BL lines exhibited rapid downregulation of the hallmark CD77 surface antigen, which, for L3055 cells, was maintained for at least 12 days after 72 hours of incubation with CD40L. With the exception of BL2, all group I BL lines were induced to express CD40 homodimers on CD40-stimulation, whereas only monomers were detected in unstimulated cells. Experiments using CD40-transfected Rat-1 fibroblasts showed that the ability to signal for dimer formation required Thr234 of CD40. For L3055 and BL29 cells, an initial 72 hours of exposure to CD40L resulted in the maintenance of homodimers for up to 14 and 10 days, respectively. There was a close correlation between the induction and duration of CD40 homodimers and the appearance of Bcl-2. For L3055 cells, which are sensitive to apoptosis-induction on BCR-engagement, exposure to CD40L for 72 hours was found to provide considerable protection from anti-IgM, which was still significant to 20 days. The implications of such sustained effects on relatively short-term exposure of tumor B cells to CD40L are discussed.

L7 ANSWER 14 OF 20 MEDLINE
ACCESSION NUMBER: 97150845 MEDLINE
DOCUMENT NUMBER: 97150845 PubMed ID: 8995381
TITLE: Heteromultimeric complexes of CD40 ligand are present on the cell surface of human T lymphocytes.
AUTHOR: Hsu Y M; Lucci J; Su L; Ehrenfels B; Garber E; Thomas D
CORPORATE SOURCE: Department of Protein Engineering, Biogen Inc., Cambridge, Massachusetts 02142, USA.. yen-ming_hsu@biogen.com
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jan 10) 272 (2) 911-5.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 20000303
Entered Medline: 19970212

AB CD40 ligand (CD40L), a 33-kDa type II membrane glycoprotein expressed primarily on activated CD4+ T lymphocytes, is responsible for the helper function of T cells on resting B cells in a non-antigen-dependent, non-major histocompatability complex-restricted fashion. Interaction of CD40L with its receptor CD40 induces proliferation of and isotype switching in B lymphocytes. Recently we solved the x-ray structure of recombinant soluble CD40L and showed that, similar to other members of the tumor necrosis factor family, CD40L indeed exists as a trimer. We now report that, under normal physiological conditions, CD40L molecules exist as heteromultimeric complexes. These CD40L complexes, made of the full length and smaller fragments of CD40L, are present on the cell surface of T lymphocytes and are capable of interacting with CD40 molecule. A prominent fragment with a mass of 31 kDa accounts for as much as half of the CD40L on the surface of Jurkat cells. N-terminal

sequence data revealed that this fragment lacks the cytoplasmic tail. A minor 18-kDa fragment of CD40L was also characterized which lacks the cytoplasmic tail, transmembrane region, and stalk region of the extracellular domain. The presence of CD40L heteromultimeric variants implies an additional regulation of the functional activity of this ligand complex.

L7 ANSWER 15 OF 20 MEDLINE
ACCESSION NUMBER: 97107144 MEDLINE
DOCUMENT NUMBER: 97107144 PubMed ID: 8949892
TITLE: Self-interaction of the major 27-kilodalton outer dense fiber protein is in part mediated by a leucine zipper domain in the rat.
AUTHOR: Shao X; van der Hoorn F A
CORPORATE SOURCE: Department of Medical Biochemistry, University of Calgary, Alberta, Canada.
SOURCE: BIOLOGY OF REPRODUCTION, (1996 Dec) 55 (6) 1343-50.
Journal code: A3W; 0207224. ISSN: 0006-3363.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 19980206
Entered Medline: 19970307
AB The RT7 gene is exclusively expressed in spermatids and encodes the 27-kDa major outer dense fiber (ODF) protein ODF27. Analysis of its amino acid structure had indicated the presence of a putative leucine zipper dimerization motif in the N-terminus and the presence of PCX repeats in the C-terminus. We had previously shown that the ODF27 N-terminal fragment can interact with full-length ODF27. We have used two different methods to analyze this interaction further. First we used fusion proteins between glutathione S-transferase (GST) and ODF27-derived fragments to show that the N-terminal half of ODF27 as well as the first 100 amino acids can interact with ODF27. A fusion protein consisting of GST and the ODF27 leucine zipper did not interact with ODF27. We found that the ODF27 C-terminal half can also interact with ODF27. The yeast two-hybrid method was next employed to analyze these interactions in vivo. We found that 1) N-terminal fragments containing the leucine zipper interact with the ODF27 N-terminus, but not with its C-terminus, 2) deletion of the leucine zipper abolished this interaction, and 3) the PCX repeats are involved in the self-interaction of the ODF27 C-terminus. The detected self-associations are weak. To analyze the molecular weight of in vitro-translated ODF27, we carried out gel filtration experiments. They show that at low concentrations, a fraction of ODF27 proteins exists as multimers while the rest are monomers whose shape deviates considerably from that of globular proteins. Our results identify regions in the N- and C-termini of ODF27 involved in self-interactions and suggest that in ODF, where high protein concentrations prevail, ODF27 can self-interact.

L7 ANSWER 16 OF 20 MEDLINE
ACCESSION NUMBER: 96257796 MEDLINE
DOCUMENT NUMBER: 96257796 PubMed ID: 8647193
TITLE: Human dendritic cells activate T lymphocytes via a CD40: CD40 ligand-dependent pathway.
AUTHOR: McLellan A D; Sorg R V; Williams L A; Hart D N
CORPORATE SOURCE: Haematology/Immunology Research Group, Christchurch Hospital and Christchurch School of Medicine, New Zealand.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1996 Jun) 26 (6) 1204-10.
Journal code: EN5; 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960805
Last Updated on STN: 19960805
Entered Medline: 19960725

AB The CD40:CD40 ligand (CD40L) interaction provides T lymphocyte-mediated help for B lymphocyte and monocyte function but has also been shown to serve as a co-stimulus for T lymphocyte activation. In this report, we studied the regulation of CD40 expression and its functional relevance for the human dendritic cell (DC) stimulation of T lymphocytes. Only a small subpopulation of directly isolated blood DC expressed CD40. However, CD40 was rapidly up-regulated by culture, and its expression was further enhanced by interleukin (IL)-1 alpha, IL-1 beta, IL-3, tumor necrosis factor-alpha and granulocyte/macrophage-colony-stimulating factor. Expression of CD40L on DC was not detected. The proliferation of T lymphocytes in an allogeneic mixed leukocyte reaction, stimulated by blood DC or epidermal Langerhans cells, was significantly reduced in the presence of the CD40 immunoglobulin (CD40Ig) fusion protein or CD40L monoclonal antibodies. Cross-linking of CD40 on directly isolated DC with mouse CD40L trimer (mCD40LT) markedly augmented CD80 and CD86 up-regulation. Nevertheless, the same cross-linking mCD40LT inhibited DC stimulated T lymphocyte proliferation. When CD40Ig was added simultaneously with CTLA-4Ig, only minimal and variable additional inhibition of DC-stimulated allogeneic T lymphocyte proliferation and IL-2 secretion was observed, compared to each fusion protein alone. These results suggest that both CD80/CD86-dependent and -independent components of DC-T lymphocyte CD40:CD40L co-stimulation exist and further emphasize that the majority of blood DC have to differentiate or be activated to express co-stimulatory molecules.

L7 ANSWER 17 OF 20 MEDLINE
ACCESSION NUMBER: 96216483 MEDLINE
DOCUMENT NUMBER: 96216483 PubMed ID: 8631992
TITLE: The CD40L promoter contains nuclear factor of activated T cells-binding motifs which require AP-1 binding for activation of transcription.
AUTHOR: Tsytsykova A V; Tsitsikov E N; Geha R S
CORPORATE SOURCE: Division of Immunology, Children's Hospital and Departments of Pediatrics, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: AI-28046 (NIAID)
AI-31541 (NIAID)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Feb 16) 271 (7) 3763-70.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960715
Last Updated on STN: 19970203
Entered Medline: 19960702
AB Four nuclear factor of activated T cells (NF-AT) binding motifs were found in the murine CD40 ligand promoter. Electrophoretic mobility shift assays using 18-base pair (bp) long oligonucleotides corresponding to the proximal site and nuclear extracts from activated T cells revealed two complexes which were inhibited by cyclosporin A and contained NF-ATc and NF-ATp. Neither complex contained AP-1 proteins. Multimers of the 18-bp oligonucleotides were not active in transient transfection assays using luciferase reporter gene constructs. In contrast, a 30-bp long oligonucleotide bound AP-1 proteins in addition to NF-AT proteins and its multimers strongly induced luciferase gene expression. These results suggested that NF-AT proteins play an important role in the expression of the CD40L gene and that their transcriptional activity requires AP-1 binding.

L7 ANSWER 18 OF 20 MEDLINE
ACCESSION NUMBER: 96198042 MEDLINE
DOCUMENT NUMBER: 96198042 PubMed ID: 8626375
TITLE: Human native soluble CD40L is a biologically active trimer, processed inside microsomes.
AUTHOR: Pietravalle F; Lecoanet-Henchoz S; Blasey H; Aubry J P; Elson G; Edgerton M D; Bonnefoy J Y; Gauchat J F
CORPORATE SOURCE: Glaxo Institute for Molecular Biology, Geneva, Switzerland.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Mar 15) 271 (11) 5965-7.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960708
Last Updated on STN: 19980206
Entered Medline: 19960624
AB CD40 ligand (CD40L) is a glycoprotein expressed on the surface of activated helper T cells, basophils, mast cells, and eosinophils. Binding of CD40L to its receptor CD40 on the B cell surface induces B cell proliferation, adhesion, and immunoglobulin class switching. We have identified soluble cleavage products of human CD40L in the supernatant of a stimulated human T cell clone. Subcellular fractionation experiments have shown that the transmembrane CD40L is processed inside the microsomes and that its cleavage is stimulation-dependent. The native human soluble CD40L is trimeric and, when used in conjunction with interleukin-4, induces B cell proliferation.

L7 ANSWER 19 OF 20 MEDLINE
ACCESSION NUMBER: 96131874 MEDLINE
DOCUMENT NUMBER: 96131874 PubMed ID: 8589998
TITLE: 2 A crystal structure of an extracellular fragment of human CD40 ligand.
COMMENT: Erratum in: Structure 1995 Dec 15;3(12):1426
AUTHOR: Karpusas M; Hsu Y M; Wang J H; Thompson J; Lederman S; Chess L; Thomas D
CORPORATE SOURCE: Biogen, Inc., Cambridge, MA 02142, USA.
CONTRACT NUMBER: AI 30361 (NIAID)
P01-AI-26886 (NIAID)
R01-CA55713 (NCI)
+
SOURCE: STRUCTURE, (1995 Oct 15) 3 (10) 1031-9.
Journal code: B31; 9418985. ISSN: 0969-2126.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960404
Last Updated on STN: 19980206
Entered Medline: 19960328
AB BACKGROUND: The CD40 ligand (CD40L) is a member of the tumor necrosis factor (TNF) family of proteins and is transiently expressed on the surface of activated T cells. The binding of CD40L to CD40, which is expressed on the surface of B cells, provides a critical and unique pathway of cellular activation resulting in antibody isotype switching, regulation of apoptosis, and B cell proliferation and differentiation. Naturally occurring mutations of CD40L result in the clinical hyper-IgM syndrome, characterized by an inability to produce immunoglobulins of the IgG, IgA and IgE isotypes. RESULTS: We have determined the crystal structure of a soluble extracellular fragment of human CD40L to 2 A resolution and with an R factor of 21.8%. Although the molecule forms a trimer similar to that found for other members of the TNF family, such as TNF alpha and lymphotoxin-alpha, and exhibits a similar overall fold, there are considerable differences in several loops including those predicted to be involved in CD40 binding. CONCLUSIONS: The structure suggests that most of the hyper-IgM syndrome mutations affect the folding and stability of the molecule rather than the CD40-binding site directly. Despite the fact that the hyper-IgM syndrome mutations are dispersed in the primary sequence, a large fraction of them are clustered in space in the vicinity of a surface loop, close to the predicted CD40-binding site.

L7 ANSWER 20 OF 20 MEDLINE
ACCESSION NUMBER: 93200072 MEDLINE

DOCUMENT NUMBER: 93200072 PubMed ID: 8095800
TITLE: A 3-D model for the CD40 ligand predicts that it is a compact trimer similar to the tumor necrosis factors.
AUTHOR: Peitsch M C; Jongeneel C V
CORPORATE SOURCE: Institute of Biochemistry, University of Lausanne, Epalinges, Switzerland.
SOURCE: INTERNATIONAL IMMUNOLOGY, (1993 Feb) 5 (2) 233-8. Journal code: AY5; 8916182. ISSN: 0953-8178.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930507
Last Updated on STN: 19950206
Entered Medline: 19930421

AB Based on the similarity in primary structure between the newly characterized ligand for CD40 (CD40L) and the tumor necrosis factors (TNFs), we have modeled a detailed 3-D structure for CD40L . We used the known structure of TNF alpha as a template for the generation of the CD40L model. The soundness of the model-building algorithms was verified by constructing a 3-D model of TNF beta and comparing it to its crystallographically determined structure. The CD40L sequence is entirely compatible with the 'jelly-roll' beta-strand structure characteristic of the TNFs. Like the TNFs, CD40L is predicted to form a compact trimer, although the interactions between monomers are distinct from those found in the TNFs. The model predicts which regions of CD40L could interact with its receptor(s) and which amino acids are essential for the maintenance of its trimeric structure.

```
=> s fasl or ox-40l or trail or apo-2l or april or vegi
      2397 FASL
         1 FASLS
      2397 FASL
           (FASL OR FASLS)
      3540 OX
         3 OXES
       122 OXEN
      3652 OX
           (OX OR OXES OR OXEN)
        13 40L
         5 OX-40L
           (OX(W)40L)
      1709 TRAIL
       655 TRAILS
      2292 TRAIL
           (TRAIL OR TRAILS)
     11699 APO
       621 APOS
     12278 APO
           (APO OR APOS)
       603 2L
        30 APO-2L
           (APO(W)2L)
     18882 APRIL
         2 APRILS
     18884 APRIL
           (APRIL OR APRILS)
         8 VEGI
L8     23513 FASL OR OX-40L OR TRAIL OR APO-2L OR APRIL OR VEGI

=> s l8 and l4
L9        11 L8 AND L4

=> d l9 1- ibib,abs

L9  ANSWER 1 OF 11    MEDLINE
ACCESSION NUMBER:  2001291746    MEDLINE
DOCUMENT NUMBER:   21267649   PubMed ID: 11374416
```

TITLE: Apoptosis in chronic rejection of human cardiac allografts.
AUTHOR: Xu B; Sakkas L I; Slachta C A; Goldman B I; Jeevanandam V; Oleszak E L; Platsoucas C D
CORPORATE SOURCE: Department of Microbiology and Immunology, Fels Institute for Cancer Research and Molecular Biology, and Temple University School of Medicine, Philadelphia, PA 19140, USA.
CONTRACT NUMBER: PO1 AI40160 (NIAID)
T32 AI07101 (NIAID)
SOURCE: TRANSPLANTATION, (2001 Apr 27) 71 (8) 1137-46.
Journal code: WEJ; 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20010625
Entered Medline: 20010621
AB BACKGROUND: We investigated the role of apoptosis (programed cell death) in the pathogenesis of chronic rejection. METHODS: Epicardial coronary arteries from cardiac allografts with chronic rejection were examined for apoptosis by the TUNEL assay. Double labeling was carried out using anti-CD3, anti-CD68, and anti-von Willenbrand factor (vWF) monoclonal antibodies. Additional immunostaining was carried using anti-Fas, anti-Fas-L, and anti-Bcl-2 monoclonal antibodies. Apoptosis-associated oligonucleosomal DNA degradation was assessed by DNA agarose gel electrophoresis. The transcription level of apoptosis-related caspase genes were determined using microarrays. RESULTS: Apoptotic cells (TUNEL+) were detected within the arterial wall and in perivascular areas. Double labeling demonstrated that apoptotic cells included T cells (CD3+), monocyte/macrophages (CD68+), and vascular endothelial cells (VWF+). Numbers and densities of TUNEL+ cells did not correlate with the degree of arterial stenosis. Apoptosis-associated oligonucleosomal DNA degradation was assessed by agarose gel electrophoresis of DNA, which showed DNA fragments of approximately 180 bp and multimers thereof (DNA laddering gel), which are characteristic for DNA fragmentation in apoptotic cells. Microarray analysis demonstrated that the apoptosis related caspases 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, were all transcribed (caspases 8, 9, and 10 were highly up-regulated). These results are consistent with the involvement of apoptosis in chronic rejection. Immunoreactivity for Fas/Fas-L was present at the sites of apoptotic cells. Immunoreactivity for Bcl-2 was present in areas with very few apoptotic cells. CONCLUSIONS: Apoptotic cells include T cells, monocyte/macrophages, and endothelial cells. Apoptosis, likely through the Fas/Fas-L system, is involved in the pathogenesis of chronic rejection in cardiac allografts.

L9 ANSWER 2 OF 11 MEDLINE
ACCESSION NUMBER: 2001116617 MEDLINE
DOCUMENT NUMBER: 20571229 PubMed ID: 11122106
TITLE: Expression of tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors and sensitivity to TRAIL-induced apoptosis in primary B-cell acute lymphoblastic leukaemia cells.
AUTHOR: Clodi K; Wimmer D; Li Y; Goodwin R; Jaeger U; Mann G; Gadner H; Younes A
CORPORATE SOURCE: Children's Cancer Research Institute, Vienna, Austria, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA.. clodi@ccri.uniwie.ac.at
SOURCE: BRITISH JOURNAL OF HAEMATOLOGY, (2000 Nov) 111 (2) 580-6.
Journal code: AXC. ISSN: 0007-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010215
AB Because tumour necrosis factor (TNF)-related apoptosis-inducing ligand (

TRAIL) (Apo2 ligand) preferentially kills malignant cells while sparing normal cells, it may be therapeutically useful against cancers, including those of haematopoietic origin. Although the activity of TRAIL has been studied in tumour cell lines and in a limited number of different primary tumours, its overall activity in a large number of uniform cases of primary tumours is not known. We therefore studied the activity of TRAIL in 29 primary precursor B-cell acute lymphoblastic leukaemia (ALL) samples. TRAIL was found to have a modest activity as it killed a maximum of 29% of ALL cells within 18 h compared with killing 75% of Jurkat cells. The sensitivity to TRAIL did not correlate with the pattern of TRAIL receptor expression or FLIP expression, as determined by Western blot analysis. The CD40 receptor, which can transduce survival signals in mature malignant B cells, was less frequently expressed on ALL cells, but incubation with an exogenous soluble CD40 ligand trimer did not rescue them from spontaneous apoptosis and did not mediate their resistance to TRAIL. Further, although ALL cells expressed TRAIL protein, they failed to kill target Jurkat cells in a TRAIL-dependent manner. Our data delineate major biological differences between mature and precursor malignant B cells and suggest a limited therapeutic role for TRAIL as a single agent in primary B-cell ALL.

L9 ANSWER 3 OF 11 MEDLINE
ACCESSION NUMBER: 2001097792 MEDLINE
DOCUMENT NUMBER: 20407128 PubMed ID: 10947965
TITLE: Functional analysis of tumour necrosis factor-alpha-related apoptosis-inducing ligand (TRAIL): cysteine-230 plays a critical role in the homotrimerization and biological activity of this novel tumoricidal cytokine.
AUTHOR: Trabzuni D; Famulski K S; Ahmad M
CORPORATE SOURCE: Laboratory of Molecular Apoptosis and Cancer Therapy, Department of Biological and Medical Research, King Faisal Specialist Hospital and Research Center, MBC-03 Riyadh 11211, Saudi Arabia.
SOURCE: BIOCHEMICAL JOURNAL, (2000 Sep 1) 350 Pt 2 505-10. Journal code: 9YO. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010201
AB We have determined that the mutation of the cysteine-230 residue to either glycine or serine in TRAIL (tumour necrosis factor-alpha-related apoptosis-inducing ligand) results in the formation of a structurally incompetent dimer and a consequent loss of apoptotic activity. Similarly, chemical modification of the thiol residues present in both reduced and Zn(2+)-depleted trimer converts TRAIL into an inactive dimer. We postulate that cysteine-230 plays a critical role in homotrimerization of this tumoricidal cytokine.

L9 ANSWER 4 OF 11 MEDLINE
ACCESSION NUMBER: 2000406082 MEDLINE
DOCUMENT NUMBER: 20341993 PubMed ID: 10882568
TITLE: A clock and trail model for somite formation, specialization and polarization.
AUTHOR: Kerszberg M; Wolpert L
CORPORATE SOURCE: Recepteurs et Cognition, CNRS URA 2182, Institut Pasteur, 25, rue du Docteur Roux, Paris Cedex 15, F-75724, France.
SOURCE: JOURNAL OF THEORETICAL BIOLOGY, (2000 Aug 7) 205 (3) 505-10. Journal code: K8N; 0376342. ISSN: 0022-5193.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008

ENTRY DATE: Entered STN: 20000901
Last Updated on STN: 20000901
Entered Medline: 20000821

AB We present some theoretical considerations about the initial process of pre-patterning during embryonic segmentation, with particular reference to somite formation. We first suggest that the pre-pattern is a stable spatial sinusoidal (or, at least, periodic) wave. The periodic wave originates from an oscillator ("clock") in the proliferative region that gives rise to the cells. At the moment the cells leave the proliferative or "progress" zone, or somewhat later, a permanent record is made of the current state of the oscillation, which cells then keep during their pre-somitic phase, before explicit somite and somite boundary formation. Thus, a trail is left behind the progress zone in the form of a spatial sine wave. Second, we also observe that the factors involved in the progress-zone clock and its wave-like trail may form multimers, which will oscillate with higher space-time frequency and thus shorter wavelengths than the monomers. Whether or not our first suggestion is correct, this phenomenon may account for multiple wavelengths in somitogenesis, and may thus encompass somite formation, but also somite polarization (half-wavelength) into anterior and posterior halves, as well as the puzzling observation that expression of her1 in zebrafish is in primordia of alternating somites, i.e. it exhibits a 2-somite wavelength.

L9 ANSWER 5 OF 11 MEDLINE
ACCESSION NUMBER: 2000396592 MEDLINE
DOCUMENT NUMBER: 20347153 PubMed ID: 10748154
TITLE: Cysteine 230 is essential for the structure and activity of the cytotoxic ligand TRAIL.
AUTHOR: Bodmer J L; Meier P; Tschopp J; Schneider P
CORPORATE SOURCE: Institute of Biochemistry, University of Lausanne and Laboratoire Cantonal, CH-1066 Epalinges, Switzerland.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Jul 7) 275 (27) 20632-7.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000816

AB Unlike other tumor necrosis factor family members, the cytotoxic ligand tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)/ Apo-2L contains an unpaired cysteine residue (Cys(230)) in its receptor-binding domain. Here we show that the biological activity of both soluble recombinant TRAIL and cell-associated, full-length TRAIL is critically dependent on the presence of Cys(230). Mutation of Cys(230) to alanine or serine strongly affected its ability to kill target cells. Binding to its receptors was decreased by at least 200-fold, and the stability of its trimeric structure was reduced. In recombinant TRAIL, Cys(230) was found engaged either in interchain disulfide bridge formation, resulting in poorly active TRAIL, or in the chelation of one zinc atom per TRAIL trimer in the active, pro-apoptotic form of TRAIL.

L9 ANSWER 6 OF 11 MEDLINE
ACCESSION NUMBER: 2000336849 MEDLINE
DOCUMENT NUMBER: 20336849 PubMed ID: 10875917
TITLE: A domain in TNF receptors that mediates ligand-independent receptor assembly and signaling.
COMMENT: Comment in: Science. 2000 Jun 30;288(5475):2328-7
AUTHOR: Chan F K; Chun H J; Zheng L; Siegel R M; Bui K L; Lenardo M J
CORPORATE SOURCE: Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: SCIENCE, (2000 Jun 30) 288 (5475) 2351-4.

Journal code: UJ7; 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000724
AB A conserved domain in the extracellular region of the 60- and 80-kilodalton tumor necrosis factor receptors (TNFRs) was identified that mediates specific ligand-independent assembly of receptor trimers . This pre-ligand-binding assembly domain (PLAD) is physically distinct from the domain that forms the major contacts with ligand, but is necessary and sufficient for the assembly of TNFR complexes that bind TNF-alpha and mediate signaling. Other members of the TNFR superfamily, including TRAIL receptor 1 and CD40, show similar homotypic association. Thus, TNFRs and related receptors appear to function as preformed complexes rather than as individual receptor subunits that oligomerize after ligand binding.

L9 ANSWER 7 OF 11 MEDLINE
ACCESSION NUMBER: 2000322672 MEDLINE
DOCUMENT NUMBER: 20322672 PubMed ID: 10866303
TITLE: Cysteine 230 modulates tumor necrosis factor-related apoptosis-inducing ligand activity.
AUTHOR: Seol D W; Billiar T R
CORPORATE SOURCE: Department of Surgery, University of Pittsburgh School of Medicine, Pennsylvania 15261, USA.. seold+@pitt.edu
CONTRACT NUMBER: GM44100 (NIGMS)
SOURCE: CANCER RESEARCH, (2000 Jun 15) 60 (12) 3152-4.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000720
AB Biologically active tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) protein is known to form a homotrimer in solution. Unexpectedly, the recombinant active human TRAIL protein purified from bacteria produced two bands (a Mr 21,000 monomer derived from the disruption of the trimer in SDS gels and a Mr 42,000 dimer) on nonreducing SDS gels. The treatment of this TRAIL protein with DTT, a reducing agent, abolished formation of the Mr 42,000 band, suggesting that the Mr 42,000 band was the result of intermolecular disulfide bridge formation. Inspection of the amino acid sequence of human TRAIL protein identified a unique cysteine residue at position 230, and subsequent site-directed mutagenesis revealed that this amino acid residue is responsible for the appearance of the Mr 42,000 dimer. The binding analysis using the TRAIL protein and a TRAIL receptor (death receptor 5) revealed that both the dimer and the trimer bind to death receptor 5 with similar affinity. Interestingly, mutation of cysteine 230 to glycine completely abolished the apoptotic activity of TRAIL protein. The disruption of the dimer in the mixture of TRAIL dimer and trimer increased the apoptotic activity slightly, suggesting that the dimer has less apoptotic activity than the trimer. Therefore, our data indicate that cysteine 230 is not only required for TRAIL function but also modulates the apoptotic activity of TRAIL by forming an intermolecular disulfide bridge.

L9 ANSWER 8 OF 11 MEDLINE
ACCESSION NUMBER: 2000117366 MEDLINE
DOCUMENT NUMBER: 20117366 PubMed ID: 10651627
TITLE: A unique zinc-binding site revealed by a high-resolution X-ray structure of homotrimeric Apo2L/TRAIL.
AUTHOR: Hymowitz S G; O'Connell M P; Ultsch M H; Hurst A; Totpal K;

Ashkenazi A; de Vos A M; Kelley R F
CORPORATE SOURCE: Department of Protein Engineering, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, USA.
SOURCE: BIOCHEMISTRY, (2000 Feb 1) 39 (4) 633-40.
Journal code: A0G; 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000309
Last Updated on STN: 20000309
Entered Medline: 20000223
AB Apoptosis-inducing ligand 2 (Apo2L, also called TRAIL), a member of the tumor necrosis factor (TNF) family, induces apoptosis in a variety of human tumor cell lines but not in normal cells [Wiley, S. R., Schooley, K., Smolak, P. J., Din, W. S., Huang, C.-P., Nicholl, J. K., Sutherland, G. R., Smith, T. D., Rauch, C., Smith, C. A., and Goodwin, R. G. (1995) Immunity 3, 673-682; Pitti, R. M., Marsters, S. A., Ruppert, S., Donahue, C. J., Moore, A., and Ashkenazi, A. (1996) J. Biol. Chem. 271, 12687-12690]. Here we describe the structure of Apo2L at 1.3 A resolution and use alanine-scanning mutagenesis to map the receptor contact regions. The structure reveals a homotrimeric protein that resembles TNF with receptor-binding epitopes at the interface between monomers. A zinc ion is buried at the trimer interface, coordinated by the single cysteine residue of each monomer. The zinc ion is required for maintaining the native structure and stability and, hence, the biological activity of Apo2L. This is the first example of metal-dependent oligomerization and function of a cytokine.

L9 ANSWER 9 OF 11 MEDLINE
ACCESSION NUMBER: 1999128052 MEDLINE
DOCUMENT NUMBER: 99128052 PubMed ID: 9930862
TITLE: Tumoricidal activity of tumor necrosis factor-related apoptosis-inducing ligand in vivo.
COMMENT: Comment in: Nat Med. 1999 Feb;5(2):146-7
AUTHOR: Walczak H; Miller R E; Ariail K; Gliniak B; Griffith T S; Kubin M; Chin W; Jones J; Woodward A; Le T; Smith C; Smolak P; Goodwin R G; Rauch C T; Schuh J C; Lynch D H
CORPORATE SOURCE: Immunex Corporation, Seattle, Washington 98101, USA.
SOURCE: NATURE MEDICINE, (1999 Feb) 5 (2) 157-63.
Journal code: CG5; 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 19990311
Entered Medline: 19990223
AB To evaluate the utility of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) as a cancer therapeutic, we created leucine zipper (LZ) forms of human (hu) and murine (mu) TRAIL to promote and stabilize the formation of trimers. Both were biologically active, inducing apoptosis of both human and murine target cells in vitro with similar specific activities. In contrast to the fulminant hepatotoxicity of LZ-huCD95L in vivo, administration of either LZ-huTRAIL or LZ-muTRAIL did not seem toxic to normal tissues of mice. Finally, repeated treatments with LZ-huTRAIL actively suppressed growth of the TRAIL-sensitive human mammary adenocarcinoma cell line MDA-231 in CB.17 (SCID) mice, and histologic examination of tumors from SCID mice treated with LZ-huTRAIL demonstrated clear areas of apoptotic necrosis within 9-12 hours of injection.

L9 ANSWER 10 OF 11 MEDLINE
ACCESSION NUMBER: 97188393 MEDLINE
DOCUMENT NUMBER: 97188393 PubMed ID: 9036978
TITLE: Lethal effect of recombinant human Fas ligand in mice pretreated with Propionibacterium acnes.
AUTHOR: Tanaka M; Suda T; Yatomi T; Nakamura N; Nagata S

CORPORATE SOURCE: Osaka Bioscience Institute, Japan.
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 Mar 1) 158 (5) 2303-9.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 19970321
Entered Medline: 19970311

AB Fas ligand (FasL) is a type II membrane protein. Binding of FasL to its receptor, Fas, induces apoptosis. Matrix metalloproteinase cleaves the membrane-bound human FasL to yield the active soluble form. Here, we have produced a large amount of human soluble rFasL using the yeast, Pichia pastoris. The purified rFasL was found to be glycosylated and to exist as a trimer. The rFasL was effective in inducing apoptosis in a Fas-expressing T cell or a fibroblast cell line. The ID50 of rFasL for mouse Fas-expressing T cells was about 0.5 ng/ml. The killing process with rFasL was quick. That is, >80% Fas-expressing mouse cells were killed within 1 h by a saturation concentration of human rFasL. Intravenous administration of 500 microg of human rFasL had a lethal effect in mice. When the mice were pretreated with Propionibacterium acnes, the subsequent injection of 30 microg of human rFasL induced hepatic failure and killed the mice within 24 h. These results indicated that the soluble human FasL is active in inducing apoptosis in vitro and in vivo, and its deleterious effect may be strengthened in patients who are suffering from bacterial infection.

L9 ANSWER 11 OF 11 MEDLINE
ACCESSION NUMBER: 95237194 MEDLINE
DOCUMENT NUMBER: 95237194 PubMed ID: 7536672
TITLE: Expression of the functional soluble form of human fas ligand in activated lymphocytes.
AUTHOR: Tanaka M; Suda T; Takahashi T; Nagata S
CORPORATE SOURCE: Osaka Bioscience Institute, Japan.
SOURCE: EMBO JOURNAL, (1995 Mar 15) 14 (6) 1129-35.
Journal code: EMB; 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950605
Last Updated on STN: 19960129
Entered Medline: 19950522

AB Fas is a type I membrane protein which mediates apoptosis. Fas ligand (FasL) is a 40 kDa type II membrane protein expressed in cytotoxic T cells upon activation that belongs to the tumor necrosis factor (TNF) family. Here, we found abundant cytotoxic activity against Fas-expressing cells in the supernatant of COS cells transfected with human FasL cDNA but not with murine FasL cDNA. Using a specific polyclonal antibody against a peptide in the extracellular region of human FasL, a protein of 26 kDa was detected in the supernatant of the COS cells. The signal sequence of granulocyte colony-stimulating factor was attached to the extracellular region of human FasL. COS cells transfected with the cDNA coding for the chimeric protein efficiently secreted the active soluble form of human FasL (sFasL). Chemical crosslinking and gel filtration analysis suggested that human sFasL exists as a trimer. Human peripheral T cells activated with phorbol myristic acetate and ionomycin also produced functional sFasL, suggesting that human sFasL works as a pathological agent in systemic tissue injury.